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Autonomic nervous system dysfunction in the course of active pulmonary tuberculosis

Gianfranco Raimondi^{a,b,1}, Silvia Contini^a, Jacopo Maria Legramante^b,
 Marialuisa Bocchino^c, Sergio Sacco^b, Marco Pallante^b,
 Mario Cazzola^{a,b,*}, Cesare Saltini^{a,b}

^aPostgraduate School of Respiratory Medicine, University of Rome 'Tor Vergata', Rome, Italy

^bDepartment of Internal Medicine, Unit of Respiratory Diseases, University of Rome 'Tor Vergata',
 Via Montpellier 1, 00133 Rome, Italy

^cDepartment of Clinical and Experimental Medicine, School of Biotechnology, University of Naples "Federico II" Naples, Italy

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Summary

Background: Functional alterations of the autonomic nervous system have been described in relation to chronic hypoxemia in chronic obstructive pulmonary diseases. Aim of the present study was to investigate the occurrence of neuro-vegetative dysfunction during active tuberculosis in the absence of hypoxemia.

Materials and methods: Fifteen patients affected by pulmonary tuberculosis under standard therapy and 17 matched controls were enrolled. Activation of the sympathetic system was induced by the tilt-up test. Systolic and diastolic arterial pressures and the R–R interval were monitored for 15 min by Finapres and ECG. The baroreflex sensitivity was evaluated by the spontaneous sequences method.

Results: Systolic and diastolic pressures were significantly higher at basal conditions and showed a less increase during the tilt test in tuberculosis patients compared to healthy controls. The basal R–R interval was shorter and its reduction during the tilt test was less evident in patients. The baroreflex sensitivity was decreased in patients at basal conditions and its reduction during the tilt test was less evident than in controls.

Conclusions: Our preliminary results suggest the presence in tuberculosis patients of an altered autonomic cardiovascular regulation, which is a reduced function of the baroreflex control of the sinus node.

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*Corresponding author: Department of Internal Medicine, Unit of Respiratory Diseases, University of Rome 'Tor Vergata', Via Montpellier 1, 00133 Rome, Italy. Fax: +39 0672596621.

E-mail address: mario.cazzola@uniroma2.it (M. Cazzola).

¹Present address: Department of Experimental Medicine, University of Rome "La Sapienza", Rome, Italy.

Introduction

Cardiovascular autonomic nervous dysfunction has been described in chronic obstructive pulmonary diseases (COPD) in relation to the onset of chronic hypoxemia.¹⁻³

Autonomic disorders have also been suggested to be responsible of clinical symptoms, like postural hypotension, syncope, and cardio-respiratory arrest, occurring during invasive procedures. It has been reported that in patients affected by tuberculosis (TB), the sympathetic nervous activity is augmented in chronic hypoxic states.⁴

However, no data exist concerning the potential effects of TB itself on the autonomic cardiovascular regulation.

Recently, large multicentre trials have been focused on the prognostic value of indexes of vagal control of sinus node. In particular, the ATRAMI study has definitively indicated that an altered baroreflex control of sinus node has prognostic value for cardiac mortality and cardiac events after acute myocardial infarction.⁵ The availability of non-invasive methods allows the easy investigation of the autonomic cardiovascular regulation. In particular, the estimate of the spontaneous baroreflex sensitivity (BRS) provides information on the baroreflex control of the sinus node by analyzing the vagally mediated RR changes which occur in response to spontaneous blood pressure fluctuations.

Aim of the present study was to investigate the baroreflex control of sinus node in patients affected by active pulmonary TB with normal oxygen saturation in basal condition and during tilt-up test, considered the gold standard for the evaluation of neurocardiogenic syncope, postural orthostatic tachycardia syndrome and dysautonomic disorders.

Materials and methods

Study population

The study population included 15 patients affected by culture-confirmed and drug-susceptible active pulmonary TB (M:F = 9:6; 6/15 smokers; mean age: 30.5 ± 5.1 yrs; mean body mass index: 22.4 ± 2.7 kg/m²; cavitory disease 9/15). Exclusion criteria were: age > 50 years, fever, coexisting valvular and/or peripheral vascular diseases, frequent atrial or ventricular premature beats, conduction defects, insulin-dependent diabetes, arterial hypertension, pericarditis and peripheral neuropathy. Patients suffering from COPD were also not included. All patients were under standard anti-TB therapy (i.e., isoniazid, rifampicin, ethambutol, pyrazinamide and pyridoxine). Mean duration of treatment was 28.2 ± 13.8 days. Seventeen healthy sex, age and body mass index-matched individuals (M:F = 9:8; 4/17 smokers; mean age: 35.8 ± 8.8 yrs; mean body mass index: 23 ± 2.5 kg/m²) were recruited among hospital staff and included as control group.

Study design

The BRS assessment was made for 20 min on supine position at rest and then for additional 20 min during passive tilt test, as previously described.⁶⁻⁸

Tilt-up test was used in order to challenge the autonomic cardiovascular regulation by inducing abrupt changes in cardiovascular parameters thus providing some information on the activity of the autonomic cardiovascular regulation. In fact the decrease in venous return that results from pooling of blood in capacitance vessels of the lower extremities during tilt-up test produces a reflex increase in orthosympathetic tone.

Briefly, patients were studied in a quiet room at ambient temperature, and were asked to relax and to avoid sleeping and talking. The electrocardiographic (ECG) signal was recorded from a precordial chest lead. Arterial blood pressures were continuously and non-invasively measured by Finapres (Finapres 2300, Ohmeda). This device has been proven to provide accurate estimates of changes of intra-arterial pressure during laboratory tests, including the BRS testing employed in the present investigation.⁹

Arterial blood pressures and ECG signals were digitalized by a converter (DAQ card 6440, National Instrument Corporation, Austin, TX, USA) and stored in a personal computer for subsequent analysis through a software developed in our laboratory using a Lab view platform (National Instrument Corporation, Austin, TX, USA).

Methods

BRS was dynamically assessed by the spontaneous baroreflex method. Details of this technique have been previously described.^{6,7,10}

Briefly, the beat-by-beat time series of systolic arterial pressure (SAP) and R-R interval were scanned by a computer to identify sequences of three or more consecutive beats in which SAP and R-R interval change in the same direction (either increasing or decreasing). A linear regression was applied to each individual sequence, similar to the technique employing bolus injections of phenylephrine, and the mean slope of the SAP/R-R interval relationship, obtained by averaging all slopes computed within a given test period, was calculated and taken as a measure of the spontaneous BRS for that period. This method allows a quantification of the baroreceptor-cardiac reflex sensitivity at the current, prevailing, levels of arterial pressure and R-R interval, and reflects vagally mediated baroreflex responses.¹¹

Statistical analysis

Comparisons between groups were performed with the unpaired *t*-test and the Mann-Whitney rank sum test. Changes within the same study group were evaluated with the paired *t*-test or the Wilcoxon signed rank test in the case of non-normally distributed variables. Data were expressed as mean value \pm SE, unless otherwise specified. A *p*-value < 0.05 was considered significant.

Results

As shown in Table 1, basal values of arterial blood pressures were higher in the group of TB patients (SAP 117.7 ± 12.1 mmHg, DAP 74.7 ± 7.4 mmHg) than in that of healthy controls (SAP 107.6 ± 9.9 mmHg, DAP 65.9 ± 8.0 mmHg), being however comprised in the physiological range.

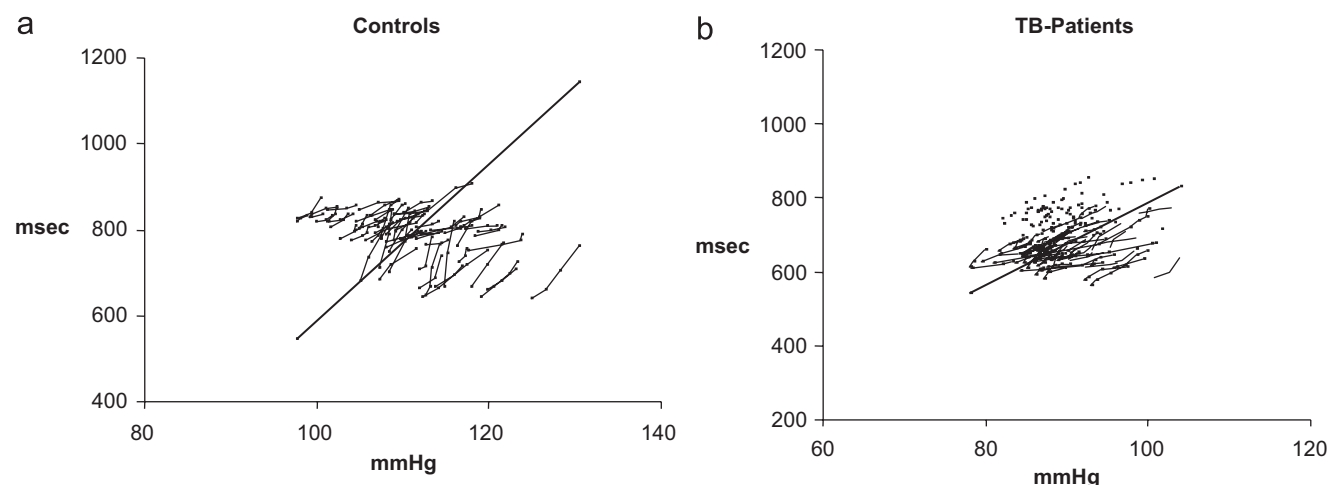


Figure 1 Shows BRS slope at rest condition in the control population (panel a) and in the TB-patients (panel b). The BRS slope is reduced in TB-patients respect to controls.

Table 1 Study population and results.

	TB-patients 9M/6F	Controls 9M/8F	p-value
Age (Years)	30.5 ± 5.1	35.8 ± 8.8	NS
BMI (kg/m ²)	22.4 ± 2.7	23.0 ± 2.5	NS
SatO ₂ (%)	97.1 ± 0.9	98.4 ± 0.8	NS
SAP (mmHg)	117.7 ± 12.1	107.6 ± 9.9	0.022
DAP (mmHg)	74.7 ± 7.4	65.9 ± 8.0	0.005
R-R (ms)	752.8 ± 141.7	904.0 ± 107.9	0.005
ΔSAP (mmHg)	5.6 ± 14.4	15.2 ± 11.5	0.045
ΔDAP (mmHg)	9.1 ± 10.2	17.1 ± 8.8	0.024
ΔR-R (ms)	-81.7 ± 192.0	-159.2 ± 58.5	0.05
BRS basal (ms/mmHg)	12.0 ± 6.8	22.2 ± 14.2	0.017
BRS tilt (ms/mmHg)	6.3 ± 3.5	8.7 ± 6.1	NS
ΔBRS (ms/mmHg)	-5.8 ± 6.3	-13.5 ± 9.2	0.001

The characteristics of the two study populations (healthy control subjects and TB-patients) are shown and the main parameters analyzed with their variation (Δ) during the tilt test. M/F = male/female; BMI = body mass index; SatO₂ = O₂ saturation; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; R-R = R-R interval; BRS = baroreflex sensitivity.

Interestingly, the basal BRS was significantly reduced in the former group than in the latter (TB patients 12.0 ± 6.8 ms/mmHg vs. controls 22.2 ± 14.2 ms/mmHg, $p = 0.017$) (Fig. 1). During the TUT, the increasing pattern of arterial blood pressures was significantly lower in TB patients (Δ SAP 5.6 ± 14.4 mmHg, Δ DAP 9.1 ± 10.2 mmHg) than in controls (Δ SAP 15.2 ± 11.5 mmHg, Δ DAP 17.1 ± 8.8 mmHg). In a similar fashion, the R-R interval showed a less significant reduction as the BRS in TB patients in response to TUT (TB patients Δ RR -81.7 ± 192.0 ms, controls Δ RR -159.2 ± 58.5 ms). No differences of the percentage of oxygen saturation (% SpO₂) at rest were observed in the two study groups.

Discussion

An impairment of the spontaneous cardiac BRS, which potentially leads to cardiovascular complications, has been

demonstrated to occur in COPD patients. In stable COPD patients abnormalities of the autonomic cardiovascular regulation have been suggested to be related to chronic hypoxemia as they may be partially reverted by oxygen administration.¹⁻³ To date, a worse oxygenation status is associated with increased cardiac vagal and decreased cardiac sympathetic activities. A similar mechanism has been reported to occur even in patients affected by TB with chronic respiratory failure.⁴

Our preliminary results suggest that the regulation of the cardiovascular autonomic system is compromised even in the case of active pulmonary TB in the absence of hypoxemia. In particular, we found that normoxic TB patients showed a significantly lower BRS as compared with healthy controls in resting conditions.

Similarly, the BRS decrease was significantly less important in TB patients as compared with healthy controls in response to tilt-up test. This test is the gold standard for the evaluation of neurocardiogenic syncope,

postural orthostatic tachycardia syndrome and dysautonomic disorders.

The cardiovascular responses to rapid postural changes reflect both changes mechanically induced by the influence of gravity on the circulatory system and those caused by the resulting nervous reflex responses. Then the tilt-up test was used in order to challenge the autonomic cardiovascular regulation by inducing abrupt changes in cardiovascular parameters thus providing some information on the activity of the autonomic cardiovascular regulation.

Such a dysfunction of the BRS may explain, at least in part, the reduction of the BP and R-R interval responses that occur during the orthostatic challenge. We suggest that the neural mechanisms regulating the cardiovascular system are less flexible in TB patients and, thus, not fully ready to challenge abrupt blood pressure and heart rate modifications. Interestingly, these abnormalities were not associated with hypoxemia. The reasons that might explain such alterations in TB patients are not readily apparent. We can speculate that any neurotropic effect of the *M. tuberculosis* may interfere with the autonomic cardiovascular regulation. In addition, although in our series no significant side effects were reported during the study period, any treatment-related influence cannot be ruled out.^{12,13} To date, pyridoxine was administered to all patients in order to prevent any disturbance of the peripheral nervous system.^{12,13}

Recent evidences suggest that leptin, that is an adipocyte-derived hormone, exerts several circulatory effects that appear to be mediated by an interaction with the sympathetic nervous system and the major reflexogenic area involved in the arterial baroreflex control.¹⁴

To date, data collected in experimental animal models and in human cardiovascular (hypertension and heart failure) and non-cardiovascular (obesity) diseases suggest that hyperleptinemia is coupled with a hyperadrenergic state.¹⁴ Regarded as a local inflammatory marker, due to the increased leptin expression in induced sputum and bronchial biopsies of COPD patients,^{15,16} serum levels are however decreased in relation to wasting, disease progression and severity.^{17,18} To date, as cachectic COPD patients show abnormalities of the autonomic nervous system (ANS), that is a depressed heart rate variability in response to both sympathetic and vagal stimuli,¹⁹ it has recently been reported that the mechanism underlying such an effect is mediated by the loss of the circadian rhythm of circulating leptin.²⁰ Finally, as disturbances of leptin metabolism have also been described in TB patients,²¹ further studies are needed to elucidate more in details if any relation between leptin and ANS modulation may occur even in such a clinical setting.

In conclusion, our results show that in patients affected by tuberculosis with normal arterial concentrations of oxygen is evident a dysfunction of the baroreflex control of sinus node both in resting conditions and in response to orthostatic stress. In those patients a particular attention should be given to the diagnostic deepening of autonomic nervous system dysfunction with tilt-up test, even in the presence of a mild or fuzzy symptomatology.

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